NASA TT F-10,410

# PROBLEMS OF PHARMACOLOGY IN SPACE MEDICINE

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Translation of "Problema farmakologii v kosmicheskoy meditsine". Paper presented at the 17th International Astronautical Congress, Madrid, 9-15 October, 1966.



NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
WASHINGTON NOVEMBER 1966

# PROBLEMS OF PHARMACOLOGY IN SPACE MEDICINE

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ABSTRACT

The authors discuss the efficient use of drugs in the preparation for and medical support of distant space flights. Some trends in the possible use of drugs during space flight are already detectable. These include stimulation of natural compensatory-adaptive mechanisms of organisms to produce increased resistance to extreme factors, prevention of infectious, neuropsychic, and somatic diseases and radiation damage, treatment of current diseases, and improving work capability (relieving fatigue and neuroemotional tension). Many drugs in conventional use and some specific drugs for space applications are treated in detail.

The prospects of carrying out prolonged space flights in orbital stations and on lunar and interplanetary spaceships have led to many new problems in /1* providing needed medical support. The development of effective means for maintaining a medical control over the crew members, predicting changes in their state of health, and diagnosing manifestations of deviations from prescribed standards and the occurrence of acute or chronic illnesses in cosmonauts; all these problems require thorough study and adequate solutions for the particular conditions obtained during each specific flight, the structural peculiarities of the spaceship, and the size and composition of the crew.

Efficient use of pharmacological drugs will play an important role in the preparation for and medical support of space flights over great distances. It is already possible to detect several trends in the possible use of drugs during space flights:

stimulating natural compensatory-adaptive mechanisms of an organism to produce increased resistance to extreme factors;
preventing infectious, neuropsychic, and somatic diseases, radiation damage, etc.
treating current diseases;
increasing capacity to do work and relieving fatigue and neuro-emotional tension.

Executing these measures will require not only those preparations which

*Numbers given in the margin indicate the pagination in the original foreign text.

can now be found in the arsenal of pharmacological means, but a synthesis of new substances which will produce the desired effect. It is already /2 necessary to develop more convenient forms of medicines and methods used to administer them with a view toward the specific features of flight conditions and preparation storing time. Probably the most applicable form of medicine under flight conditions will be tablets and single-use syringes.

The arsenal of medicines and medical instruments on board a spaceship will be determined by the nature and duration of the flight, the possible presence of a physician in the crew, size and weight capabilities, and several other factors.

As is known, on American and Soviet spaceships which have already carried out space flights there were included in the medical supplies analeptics, analgesics, antiradiation drugs, and many others (ref. 69). G. Cooper during his last orbit used a syringe to inject in his body dextro-amphetamine sulphate (dexedrin), although there was no indication that his mental or physical condition called for a stimulus (ref. 53). As C. Berry has pointed out, a substance of this type is capable of relieving possible fatigue in astronauts to a great extent and of raising their capacity to do work. The author attaches particular importance to the use of stimulants during prolonged space flights and also in various "critical situations."

There is no doubt that during prolonged flights there may occur symptoms which call for the use of medicine and this will require careful diagnosing of these symptoms, and consequently, a well-considered approach to assembling on-board medical cabinets.

Along with making a determination of possible medical symptoms for which medicines must be administered, it is no less important to study the nature of the changes in the reactions of an organism under the influence of different factors encountered during space flight and the combined effect which they may have since "...a single pharmacological preparation may prove to be either medicine or poison depending on the state of the organism."* This statement, it seems to us, finds confirmation in our data about changes in reactions to drugs during the after-effects of exposure to acceleration (ref. 36).

It follows that a study of the specific features of the effects of drugs in ground laboratories with simulation of the conditions obtaining during space flight (effects of acceleration, weightlessness, prolonged isolation, etc.) and possible emergency situations (change in gas medium, effects of ionizing radiation, disruption of feeding regime, and others) is not only an important but extremely essential stage in preparing for prolonged flights. A similar idea is expressed by G. B. Griffenhagen (ref. 62).

Below there is given information which concerns two main points of /3 the overall problem of pharmacology during space flights; increasing the resistance of an organism to extreme factors of flight and description of the

*N. V. Vershinin. Farmakologiya, 1952, p. 5.

reactivity to drugs when certain flight conditions are simulated.

Pharmacology may be one of the important means of increasing resistance of an organism to the effects of extreme factors of flight. At the present time there are available enough facts to show the possibility and advisability of using medicines for these purposes. Moreover, during past flights some aspects of this problem, as indicated above, were actually encountered (refs. 53, 69).

Of the different factors encountered during space flight those which are most deserving of attention from the point of view of possibly using drugs to increase the resistance of an organism are the effects of acceleration, weightlessness, radiation, and hypoxia.

The need to develop various agents to increase the resistance of an organism to the effects of acceleration, including drugs, is conditioned first of all by the possibility of occurrence of situations wherein the extent and duration of the effects of acceleration may reach the limits of physiological tolerance and lead not only to a great decrease in the pilot's ability to do work but also to consequences which are harmful to his health.

Attempts to use drugs to increase the resistance of an organism to the effects of acceleration have been made in tests conducted abroad as well as at home (ref. 2, 10, 11, 25, 31, 41, 42, 55, 56, 63, 68). However, up to the present time these tests have not passed beyond the confines of laboratory experiments conducted using animals. Furthermore, the results of such tests have been contradictory even when one and the same substance was used.

The authors of this article tried preparations in many pharmacological groups (table) in experiments on different kinds of animals. The results of the tests showed that by changing functional condition it is possible with drugs to increase considerably the resistance of an organism to the effects of acceleration acting in a transverse direction. When this is done a favorable effect can be produced by various preparations which differ in the nature of their effects: narcotics and analeptics, those which have an overall tonic effect and sedatives, cardiovascular agents, and others. The degree to which the effect is expressed depends on the nature of the preparations, the doses, and the way in which they are used and for how long. The most favorable results are obtained by administering strychnine, several sympathomimetic agents (phenamine, adrenalin, noradrenalin), and narcotics. The use of the substances which have been listed in optimal doses has decreased the fatality rate of animals and the degree of disruption of cardiac activity caused by /4 effects of acceleration (Fig. 1) (refs. 8, 13).

Many other authors have also obtained positive information on the feasibility of using medicines to increase resistance to the effects of acceleration (refs. 9, 24, 41, 42, 67, and others).

Thus, there is complete justification to assert that the use of drugs is a promising and important way to increase the resistance of an organism to the effects of acceleration. In this connection a question arises about the selection of the most suitable preparations, their medicinal form, and the ways

to administer them for practical use in space. In finding an answer to this question it seems to us that two circumstances must be borne in mind, that is, the stages and conditions of flight and the pharmacological properties of the preparations.

Table The Influence of Pharmacological Means on the Resistance of Animals to the Effects of Acceleration Acting in a Transverse Direction

| Preparations | Results of Test |
|---|---|
| Narcotics (thipental sodium, chloral hydrate, and others) | In small doses--increase the resistance to effects of acceleration and in large doses decreases it |
| Analeptics (caffeine, corazole, and others) | No significant effect |
| Phenamine, strychnine | In optimal doses increase resistance |
| Phenatine | Lowers resistance |
| Vascular agents (adrenalin, noradrenalin, ephedrine) | Increases resistance |
| Nitroglycerine, dibazol | No significant effect |
| Cardiac glucosides (strophanthin-K | Increases resistance |
| Antiradiation substances (cystamine and cysteamine) | Lower resistance |

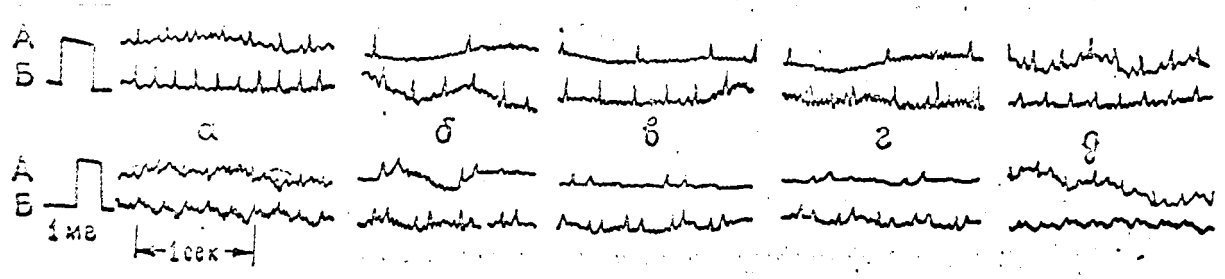


Figure 1. Electrocardiograms of rabbits subjected to the effects of acceleration acting in a transverse direction in control tests (A) and after a preliminary injection of strychnine (B):

a--prior to the effects of acceleration; b, c, d--at the end of the 1st, 3rd, and 6th minutes; e--2 minutes after effects were felt. 1--A; 2--B; 3--a; 4--b; 5--c; 6--d; 7--e; 8--1 mv; 9--1 sec.

During the first stage of a flight (spaceship liftoff) it is hardly necessary to use special medicines inasmuch as the training cosmonauts receive on the ground is entirely adequate to help them withstand the effects of acceleration satisfactorily. When a spaceship returns to Earth symptoms may occur which call for the use of drugs. First of all it must be borne in mind that after hypodynamia resistance to the effects of acceleration is lowered (refs. 32, 50). This circumstance will apparently have particular significance during prolonged space flights. Preparatory introduction of these drugs may be completely justifiable.

It is also necessary to bear in mind the possibility of emergency situations which will entail an abrupt increase in the gradient of strain to critical values due to acceleration. This will require taking appropriate /6 measures involving rapid administering of medicines.

Bearing in mind available information about the effects of medicines on the resistance of an organism to the effects of acceleration and the pharmacological properties of different preparations it appears likely that the most appropriate for the purposes which have been indicated are several sympatomimetric agents and agents having an overall tonic effect (phenamine, strychnine, securinine, and others). Such preparations, in addition to their ability to increase resistance to the effects of acceleration, have many other properties which are exceedingly useful under conditions of space flight (refs. 3, 27).

The use of narcotics and tranquilizers under these conditions would hardly be advisable since they either decrease resistance to the effects of stress (refs. 13, 64) or have properties which are undesirable for the particular activity of cosmonauts. Recommendations about the use of tranquilizers during space flight (ref. 69) must be accepted only after making appropriate modifications. Such substances may be used in case of need but never just prior to a spaceship landing on Earth.

Information which is available at the present time gives evidence of the possibility of large changes in the different systems of the organism under conditions of weightlessness (refs. 16, 17, 30, 47, 48, 49, 59, 61, 65, 66, and others). The nature of these disruptions and the degree to which they are expressed can vary and depend on many circumstances such as the conditions and duration of flight, the level to which cosmonauts have been trained to withstand the specific effects of weightlessness, reactivity of the vestibular analyzer, and so on. In some cases changes predominate in the cardiovascular system conditioned by prolonged hypodynamia and a decrease in afferent effects and in other cases sensory-vegetative disorders which result in the complex of symptoms typical of motion sickness (seasickness) predominate.

For the purpose of preventing and treating these disorders which have been mentioned the use of medicinal agents on spaceships is completely justified. The selection of preparations must be based on the varying nature of the disorders which occur. Thus, with a lowering in the tonus of the cardiovascular system or orthostatic disruptions several analeptics can be used successfully (phenamine, caffein, and others) and substances which give an overall tonic effect (strychnine, securinine, preparations derived from ginseng, spiny

eleuthracoccus, and others). With the occurrence of the seasick syndrome a favorable effect may be obtained by introducing central cholinolytics [metamizil] (2-(diethylamino) propyl benzilate hydrochloride), pentaphene, and others) and several adrenergic blocking agents (aminazine and others). Unquestionably special complex preparations which have an effect on various links of the pathogenesis of the seasick syndrome (cholinolytics and adrenergic blocking agents, stimulants of the central nervous system, antihistamines, and several others) will prove to be more effective.

Although at the present stage of development of radiobiology the problem of increasing the resistance of an organism to ionizing radiation with the help of drugs has found a largely positive solution the recommendations which are /7 made cannot be used completely under conditions of space flight. This is due first of all to the complexity of the spectrum of cosmic radiation whose mechanism of biological action has not yet been sufficiently studied. Moreover, under conditions of space flight an organism is subjected to other factors which act in varying combinations and sequences. This will affect the complexity of the pathophysiological complex of symptoms of the disorders which occur due to these factors. Therefore, the problem of finding drugs which provide protection against radiation and which are suitable for the particular conditions of space flight requires a special solution.

Many preparations are now known which have been used with success in clinical radiation therapy (cysteamine, cystamine, AET, serotonin, and others). Some of them (cysteamine, cystamine) probably can be included in on-board medical supplies as agents for preventing radiation damage. However, it should be borne in mind that radiation protection preparations which are known to be effective lower the resistance of an organism to the effects of other flight factors, specifically the effects of acceleration and vibration (ref. 43). Therefore, the indicated substances should probably be used in conjunction with other agents which would serve to lessen the unfavorable effects of the preparations intended to provide protection against radiation on the reactivity of an organism.

The problem of increasing the resistance of an organism to oxygen insufficiency under the conditions obtaining during space flight is a pressing one because of the possible occurrence of emergency situations. Using medicines under such circumstances will probably prove to be necessary. Information in available literature gives evidence of the advisability and promise of using drugs for increasing the resistance of an organism to oxygen insufficiency (refs. 1, 14, 18, 19, 29, 39, 40, and many others). Apparently the most effective is complex use of preparations which serve to decrease the need of tissues for oxygen (tranquilizers, narcotics, antioxydants) and agents which have a tonic effect on the vital functions of an organism (stimulants of the central nervous system, cardiovascular stimulants, and others). The possibility of using the method of hybernation should be borne in mind (refs. 15, 23, and others). However, the question of practical use of medicines for increasing the resistance of an organism to oxygen insufficiency as applicable to the conditions obtaining during space flight requires further study.

Therefore, included among the medicinal agents in the medical supplies of

a spaceship should be a group of preparations which are intended especially for increasing the resistance of an organism to factors of space flight. Moreover, it is necessary to bear in mind the possible occurrence in members of a crew of illnesses which are not brought on by stress factors. For preventing and /8 treating such changes in an organism it is advisable to have in the medical supplies of flying craft antibacterial agents having a wide spectrum of action, antipyretics, analgesics, disinfectants, and others. The selection of agents and their medicinal forms will be determined by the conditions and purposes of each particular flight.

As was shown above, pharmacology is acquiring ever increasing importance in the exploration of space. Principal attention is being devoted to a consideration of the purposes and methods of using medicines for preventing and treating possible sickness among members of the crew and also for increasing their physical and mental ability to work during flight (refs. 53, 60, 69).

In our opinion very little attention is being devoted to the peculiarities of pharmacological dynamics of various preparations when they are introduced into an organism with a changed functional state. Numerous scientific tests in the past few years in various countries, mainly in the Soviet Union and the USA, have made it possible to obtain much information which is important in theoretical and practical respects in revealing the physiological mechanisms of changes in the organisms of animals and man under the influence of such flight factors as acceleration, vibration, ionizing radiation, prolonged hypodynamia, and others. All this indicates that, depending on the specific situation obtaining in flight and on the time at which the need to use medicines occurs, it is possible to encounter substantial shifts in the functional state of an organism and, consequently, possible changes in the ordinarily adequate reaction of an organism to one medicinal agent or another. The importance of the initial reactivity of an organism to the use of medicines is well known to pharmacologists. There are countless examples wherein due to the influence of factors in an external medium the sensitivity of an organism to drugs undergoes significant changes and in many cases acquires a pathological nature. For example, therapeutic doses of cardiac glucosides may have a toxic effect after prolonged hypoxia (ref. 26) or transverse acceleration of long duration (ref. 36); motion sickness increases sensitivity to apomorphine greatly (ref. 38); and so on. In this connection the need for paying very close attention to the problem of reactivity in space medicine is quite obvious when we are dealing with an organism being exposed to many factors in its environment to which it is not accustomed and for which it has apparently not yet developed protective-adaptive reactions. This statement is confirmed by available scientific information about the effect on an organism of such flight factors as radiation, acceleration, and a changed gas medium. The fact should also be borne in mind that many important questions in the field of space medicine /9 have been very little studied. Among the most important of them is the problem of physiological effect of prolonged weightlessness.

What factors of space flight should be borne in mind in studying the peculiarities of reactivity of an organism? It seems everything new that the organism encounteres under conditions that are unusual for its vital activity, namely:

dynamic factors (acceleration due to ascending and descending, angular acceleration, vibration, weightlessness);

factors conditioned by peculiarities of the design of flying craft (changed hygienic parameters of the environment, limited mobility, factors affecting eating and drinking, and so on);

factors of outer space (different kinds of ionizing radiation from the radiation belts of the Earth, solar flares, and others);

factors conditioned by the specific features of the vital activity of cosmonauts (nervous and mental tension associated with monotonous operator activity, lack of customary daily schedule, prolonged stay in chamber of limited size, uniformity of surrounding situation, greatly limited afferent perception, and others).

Naturally the combined effect of the factors which have been indicated, especially during prolonged space flight, can cause substantial shifts in the functional state of various systems of an organism and thereby change the reactivity to medicinal agents.

The authors of this article have at their disposal many facts which give evidence of the changes in the pharmacodynamic effects of preparations from different groups upon introduction of them into an organism exposed to the effects of acceleration acting in a transverse direction and a changed gas medium. In this regard it has been demonstrated that the direction of the change in the response reaction of the organism to the introduction of the medicine may vary and depend on many conditions . The chief ones among them are the following:

intensity and time of action of factor;

primary effect of it on one physiological system or another of an organism;

species, sex, age, and constitutional features of the organism itself;

pharmacodynamic properties of the preparation.

Tests which were conducted by the authors of this article on animals have made it possible to establish a relationship between a change in the reactivity to a medicine and manifestation of changes in an organism caused by a preceding effect of acceleration acting in a transverse direction. For example, accelerations accompanied by significant disruptions in cardiac activity are accompanied by a subsequent abrupt increase in sensitivity of long duration (up to 2 hours) to cardiac glucosides (strophanthidin-K, convaside), narcotics /10 (barbiturates of brief duration, ether, chloral hydrate, and others), and several other preparations. At the same time such effects decrease the sensitivity of the organism to several analeptics (caffeine, corasole, cytitone, and others). Changes in the course of reactivity were found in the case of adrenalin. Depending on the intensity of the effects of acceleration and

the specific features of the reaction of the organism during rotation on a centrifuge the period of after-effects was characterized by an increase, decrease, or inversion of the pharmacological effect of the preparation (Fig. 2). The results obtained, in our opinion, are of great importance since they make it possible not only to understand more thoroughly the mechanism of physiological disruptions in an organism but to recommend with a firmer basis the use of medicinal agents applicable to the specific conditions in which this need arises.

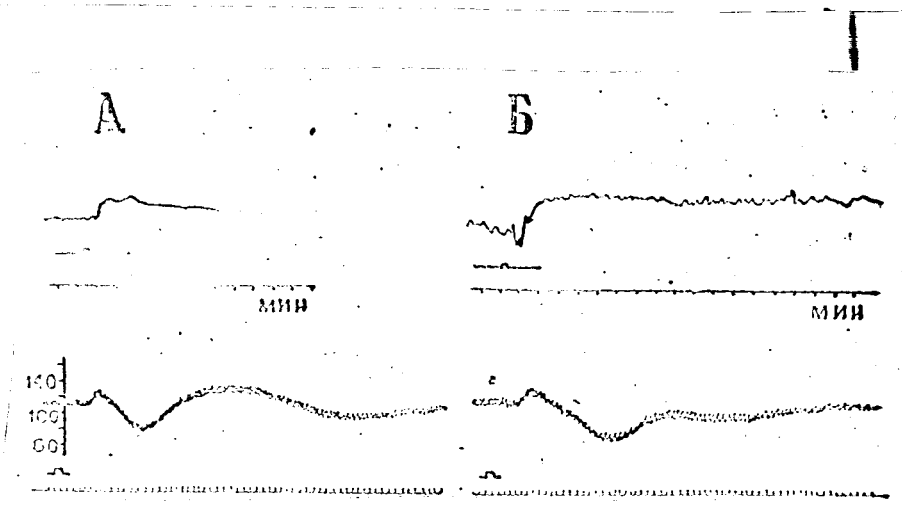


Figure 2. Specific features of reaction of coronary blood flow (above) and blood pressure in the femoral artery (below) to the intravenous introduction of adrenalin 0.002 mg/kg prior to start (A) and 15 min. after (B) effects of acceleration of 12 G acting in a transverse direction. 1--min.

Similar information is available with respect to the effect on reactivity of an organism to pharmacological preparations of a changed gas medium. The experiments conducted by N. M. Dmitriyeva (ref. 26) and other authors show convincingly that hypoxia increases markedly the sensitivity of an organism to cardiac glucosides. Brief as well as prolonged hypoxia leads to a change in the reactivity of an organism with respect to the effects of radiation (refs. 5, 6) and the duration of several infections (ref. 44). In this connection there can be found in available literature information on the role of a hyperoxide gas medium in intensifying the effect of several drugs /11 (ref. 45 and others).

In this way a change in the partial pressure of oxygen in the gas mixture being inhaled is accompanied by marked changes in the reactivity of the organism with respect to many agents, including several medicinal preparations.

The information obtained from our tests showed that a change in the content of the carbon dioxide in the gas medium being inhaled is also accompanied by significant deviations in the sensitivity of an organism to drugs. The direction and degree of manifestation of the changes in reactivity were determined by the conditions indicated above (duration and intensity of

effect, specific features of pharmacodynamics of the preparation, and others) (Fig. 3).

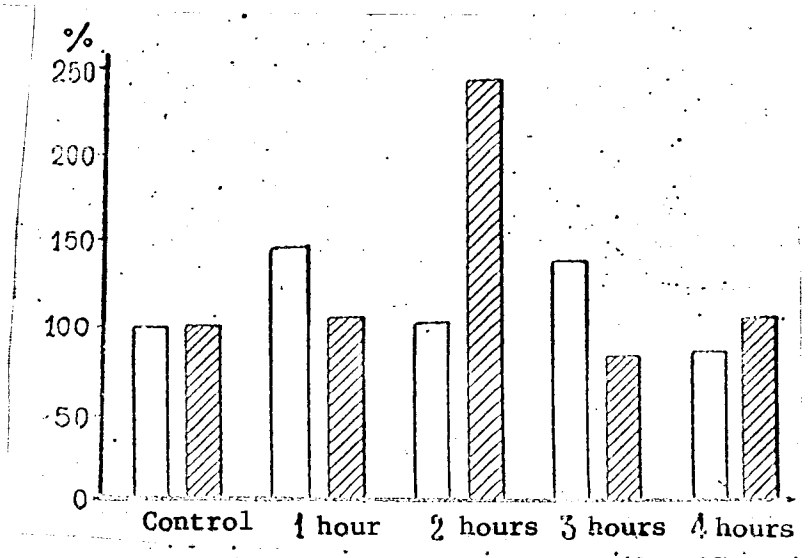


Figure 3. Effect of hypercapnic gas mixture (8--10% $CO_2$) on the duration of ethereal (white columns) and intranarcotic (shaded) narcosis in white mice: ordinate shows duration of narcosis in % of control data; abscissa shows time of stay in gas medium.

Information on the effect of reactivity of an organism produced by combinations of hypercapnia and hypoxia is of definite interest. The authors of this article have conducted some tests in this respect.

Modern space vehicles and also the prospects of having cosmonauts work in open, supportless space do not preclude possible effects of prolonged angular accelerations and other effects leading to the motion sickness syndrome. /12 Questions of pharmacological prevention and treatment of motion sickness have long since been answered but insufficient attention has been paid to the importance of this factor from the standpoint of possible change in the reactivity of an organism due to the effects of such sickness. Tests conducted by our colleague, I. D. Pestov, (refs. 37, 38) established the fact that under the influence of motion sickness a change in the functional tonus of the vomitory center occurs sooner than do other physiological changes and as a result of this the sensitivity of the organism to apomorphine is greatly increased. Apparently the functional changes in the central nervous system are not limited to the vomitory center and the use of medicines from the various pharmacological groups will make it possible to study more completely the specific features of an organism under these conditions.

The great difficulty of reproducing weightlessness under laboratory conditions is the principal reason for our limited knowledge on this subject. In recent years prolonged hypodynamia in a medium ordinarily used for immersion

has been used by various researchers as stimuli which model weightlessness. Individual attempts have been made during such experiments to study the reactivity of an organism to various medicines (ref. 70). However, this work has been limited by the problem of using mediators of the vegetational nervous system without devoting attention to the reactivity of the cardiovascular system to medicines, the use of which may be directed toward maintaining an adequate level of cardiac activity and tonus of the peripheral vessels. Further investigation will make it possible to throw light also on these questions which are of unquestionable great practical importance.

Radiation is one of the most thoroughly studied factors of space flight as far as its effect on the reactivity of an organism is concerned. It has been established as the result of numerous experiments that ionizing radiation may lead to disruption in the functioning of an organism. At the same time there are to be observed marked changes in the adaptive-regulatory functions of the nervous and endocrine systems which, most importantly, condition shifts in the reactivity of an irradiated organism to various factors in an external medium, including reactivity to medicines (refs. 7, 21, 22, and many others). On the basis of many experiments which have been conducted it can be considered to be firmly established that the reactions of an organism which has been damaged by penetrating radiation to medicinal preparations depends on the degree of severity of the damage and the period over which it has developed. For example, during the first few hours after the overall effects of ionizing radiation have been suffered the narcotic effect of derivatives of barbituric acid is noticeably weakened (refs. 20, 28, and others). During intense periods of ionizing affection the sensitivity to barbiturates is much greater. Convincing data have been obtained with respect to the reactivity of an irradiated organism to ether, nitrous oxide, and several other narcotics (refs. 33, 46, and others). The reaction of /13
an organism to cardiovascular agents when ionizing affection is being experienced also often proceed differently than in a healthy organism. For example, in the initial and latent period of radiation damage the vasoconstrictive effect of adrenalin, pituitrin, and several other substances is lessened and when radiation damage is intense, the effect is increased (refs. 12, 35, 51, 54, and others).

Important information is available on the change in the nature of the reaction of an organism to medicinal substances from the groups of analeptics, stimulants of the central nervous system and hempopiesis, chemotherapeutic agents, diuretics, and others.

The information which has been presented gives evidence of the fact that radiation, one of the important stress factors of space flight, can to a significant degree change the reactivity of an organism to many medicinal substances. Knowledge of the effect of pharmacological preparations at various stages of ionizing damage is extremely essential for selecting the best way to use them and to prevent possible complications.

Hence, the information we have obtained from our experiments and also information in the literature shows convincingly that even the isolated effects of different stress factors in space flight are accompanied by large

changes in the reactivity of an organism to medicines. The results of experiments show that questions of reactivity have great practical importance for space pharmacology. Indeed, without knowledge of the specific features of the effect of preparations during the various stages of space flight medicinal effects which have been found under normal conditions on the Earth may not only fail to produce the desired therapeutic effect but may also lead to consequences which are harmful to the organism. The importance of this assertion is even greater due to the fact that it is difficult to provide for observation by a physician of the reactions of an organism to the medicines introduced and it may prove impossible to offer qualified and specialized medical aid.

Close attention should be paid to studying the nature of the effect on an organism of a complex of stress factors due to space flight, especially to the changes which occur in reactivity under these conditions. Individual reports about the complex effect on an organism of a change in temperature and acceleration (ref. 58), hypoxia acceleration (refs. 34, 57), ionizing radiation and acceleration (ref. 4), and also several other combinations show the need to broaden investigation in this field for the purpose of studying the nature of the reactivity of an organism under conditions closely simulating actual space flight.

Hence, the problem of creating a new field of knowledge,--"space pharmacology", which has been advanced by many researchers (refs. 9, 36, 52, 69), is deserving of close attention. The principal tasks of space pharmacology /14 should be:

searching for medicines which increase the resistance of an organism to the unfavorable effects of flight factors;

studying the nature of the pharmacodynamics of various preparation against a background of changed reactivity;

developing doses and methods for introducing various medicines under the conditions obtaining during space flight;

using drugs (as analyzers of physiological functions) for identifying the mechanisms by which flight factors act on an organism.

Solving these tasks, which are so important for space flight, can be done successfully only on condition that representatives of various specialties such as pharmacologists, chemists who specialize in synthetic methods, physiologists, and clinicists be drawn into the work.

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